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Registration Action Branch 3, Health Effects Division (7509C) **Date**_____

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TXR # 0052517

DATA EVALUATION RECORD

STUDY TYPE: Fourteen Day Oral Toxicity [feeding study]-Rat

PC CODE: 099100 **DP BARCODE: D301775**
DECISION NO.: 335881

TEST MATERIAL (PURITY): Pyraclostrobin (BAS 500 F; 99.0 % a.i.)

CITATION: Mellert, W., Deckardt, K., Gembardt, C., and van Ravenzwaay, B. (2003) BAS 500 F Determination of Iron in urine and Serum of Wistar Rats: Administration of the Diet over 14 Days. BASF, Experimental Toxicology and Ecology, 67056 Ludwigshafen/Rhein, Germany. Project No. 48C0494/96216. BASF Document No. 2003/1009534. April 10, 2003. MRID 46016401. Unpublished.

SPONSOR: BASF, Experimental Toxicology and Ecology, 67056 Ludwigshafen/Rhein, Germany.

SUMMARY: In a non-guideline14-day oral toxicity study (MRID 46016401), pyraclostrobin (BAS 500 F; 99.0% a.i; Batch No. CP 029053) was administered to 10 adult Wistar [CrlGlxBrl Han:WI] rats/sex/dose in the diet at concentrations of 0, 50, 500, or 1500 ppm (equivalent to 0, 3.8, 33.9, or 73.9, mg/kg bw/day, respectively, in males and 0, 4.1, 37.4, or 78.3 mg/kg bw/day, respectively, in females). Animals were examined twice a day (or once a day on week ends) for clinical signs. Serum iron and transferrin concentrations were measured in blood from non-fasted animals on days 7 and 14; iron was also measured in the urine on day 15. In addition, food intake was determined at days 7 and 14 and body weights were recorded at days 0, 7 and 14.

There were no treatment related clinical signs or mortalities but body weights and food consumption were affected at the high and/or mid dose groups (Table 1). At days 7 and 14, mean body weight was decreased in males given pyraclostrobin at 500 (by 6%, $p<0.05$) and 1500 ppm (by 20%, $p<0.01$) as well as in females of the 1500 ppm group (13-14%, $p<0.01$). Relative to initial values, the day 14 body weights of the 1500 ppm male and female dose groups were off by 10 and 5.8 g, respectively. Relative to control values, the 500 ppm male and female groups

also had decreased body weight gain of about 40% and 14%, respectively. These findings were accompanied by decreased food intake at both days 7 and 14 in the 500 ppm male (by 10-20 %, $p<0.01$) and female (by 7-16%, $p<0.05$ or <0.01) groups as well as the 1500 ppm male and female dose groups (by 35-59%, $p<0.01$). Generally, the effects on body weight and food intake were more pronounced in males than females and at day 7 than at day 14 (Table 1).

Serum iron concentrations were decreased in a dose- and time- dependent manner by as much as 50% in males given pyraclostrobin; treated females also had lower serum iron levels but the trend and magnitude (≤22%) were less pronounced than in males (Table 2). There were slight or no biologically meaningful treatment related changes in levels of serum trasferrin, a beta$_1$ globulin that plays a key role in iron transport in the body (Table 2). Also, there were minimal or no variations in urinary iron concentrations in all treated male and female groups (Table 3). These findings combined indicate that decreased serum iron concentration is not a consequence of diminished transport and/or enhanced excretion. The study, however, did not explore the possible effect of pyraclostrobin on intestinal iron absorption. Nonetheless, the EPA reviewers believe that diminished serum iron is more likely due to malnutrition, rather than being directly caused by pyraclostrobin, since there seems to be a concordance between serum iron levels and food consumption.

In conclusion, this non-guideline14-day rat study was not designed to characterize the toxicity of pyraclostrobin nor was it intended for risk assessment purposes. Its stated objective "was to determine the level of iron in serum and urine after oral administration of BAS 500 F." The study is considered acceptable/non-guideline and is useful for its intended purposes.

COMPLIANCE: The study was not conducted in compliance with GLP regulations. The study report had statements of No Data Confidentiality Claims and No Data Quality Assurance.

TABLE 1. Average body weight, body weight gain, and food intake during 14 days of treatment with pyraclostrobin [a]

Dose [ppm]	Body weight (Mean±S. D.), g			Total weight gain[c], g	Food Consumption (Mean±S. D.), g/day	
	Day 0	Day 7	Day 14		Day 7	Day 14
Males						
0	237.6 ± 9.3 8.252.06	268.1 ± 13.9	285.7 ± 18.0	48.1	21.8 ± 1.2	20.1 ± 1.4
50	234.7 ±7.2	261.7 ± 10.5 (97.6)[b]	277.9 ± 15.1(97.3)	43.2 (89.8)	21.0 ± 0.9 (96.3)	19.4 ± 1.4 (96.5)
500	239.2 ± 6.7	253.1 ± 9.7 (94.4)*	268.4 ± 13.4 (93.9)*	29.2 (60.7)	17.4 ± 1.6 (79.8)**	18.0 ± 1.4 (89.6)**
1500	236.3 ± 7.5	216.5 ± 9.5 (80.8)**	226.3 ± 10.8 (79.2)**	-10.0	9.0 ± 1.6 (41.3)**	12.9 ± 1.2 (64.2)**
Females						
0	167.4 ± 5.4	178.2 ± 8.7	187.2 ±8.4	19.8	15.6 ± 1.0	14.9 ± 0.7
50	165.2 ± 5.6	178.0 ± 10.1 (99.9)	188.2 ± 11.1 (100.5)	23.0 (116.2)	15.4 ± 0.9 (98.7)	14.7 ± 1.1 (98.7)
500	167.1 ± 7.7	175.8 ± 8.1 (98.7)	184.1 ±8.2 (98.3)	17.0 (85.9)	13.1 ± 1.1 (84.0)**	13.8 ± 0.9 (92.6)*
1500	166.7 ± 6.2	155.1 ± 8.9 (87.0)**	160.9 ± 6.2 (86.0)**	-5.8	6.9 ± 1.2 (44.2)**	9.7 ± 0.8 (65.1)**

[a] Data obtained from pages 31-34, MRID 46016401.
[b] Data in parenthesis are percent of control.
[c] Total weight gain values are calculated by reviewer.
*, ** Significantly different from control at p <0.05 or <0.01, respectively.

TABLE 2. Serum iron and transferrin findings during 14 days of treatment with pyraclostrobin [a]

Dose [ppm]	Iron, µmol/l (Mean±S. D.)		Transferrin, g/l (Mean±S. D.)	
	Day 7	Day 14	Day 7	Day 14
Males				
0	47.0 ± 13.5	54.5 ± 9.8	5.5 ± 0.3	6.4 ± 0.8
50	44.8 ± 6.7 (95.3)[b]	46.7 ± 6.6 (85.7)	5.3 ± 0.4 (96.4)	5.8 ± 0.6 (90.6)
500	36.6 ± 5.3 (77.9)	37.7 ± 5.2 (69.2)**	5.5 ± 0.4 (100.0)	6.1 ± 0.8 (95.3)
1500	34.9 ± 3.1 (74.3)*	27.4 ± 4.4 (50.3)**	4.7 ± 0.4 (85.5)**	5.9 ± 0.5 (92.2)
Females				
0	59.1 ± 8.5	53.6 ± 4.2	5.4 ± 0.7	5.9 ± 0.7
50	60.1 ± 14.1 (101.7)	58.3 ± 12.2 (108.8)	5.2 ± 0.3 (96.3)	5.7 ± 0.7 (96.6)
500	46.5 ± 6.4 (78.7)**	45.6 ± 9.0 (85.1)*	5.6 ± 0.5 (103.7)	6.1 ± 0.6 (103.4)
1500	57.5 ± 15.6 (97.3)	42.0 ± 9.9 (78.4)**	4.9 ± 0.4 (90.7)	5.6 ± 0.7 (94.9)

[a] Data obtained from pages 37-38, MRID 46016401.
[b] Data in parenthesis are percent of control calculated by reviewer.
*, ** Significantly different from control at p <0.05 or <0.01, respectively.

TABLE 3. Urinary iron findings (nmol) after 15 days of treatment with pyraclostrobin [a]

Dose (ppm)	Males	Females
0	4.0 ± 1.4 [b]	2.6 ± 0.9
50	3.3 ± 1.5	2.4 ± 1.1
500	2.7 ± 1.2	2.8 ± 1.5
1500	3.6 ± 4.4	2.9 ± 1.2

[a] Data obtained from pages 39-40, MRID 46016401.
[b] Values are mean ± SD.